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Alkali metal salts-assisted coupling reaction between fluorinated benzyl electrophiles and alkenylboronic acids

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We have developed a versatile transition metal-free cross-coupling reaction between fluorinated benzyl electrophiles and alkenylboronic acids in the presence of the equivalent amount of alkali metal salts such as K_3PO_4 . This transition metal-free protocol gives good chemical yields for a wide range of substrates and demonstrates good functional group tolerance.

Due to the unique properties of fluorine, such as its small size and the metabolically resistant C–F bond, the selective substitution of hydrogen by fluorine has become an important strategy in medicine, agrochemistry and material research.¹ More specifically, organic compounds containing the trifluoromethyl motif, especially arenes containing the α -trifluoromethyl motif are especially common in agrochemistry and pharmaceuticals.² Examples include Efavirenz (HIV-RT inhibitor),³ pesticidal agents,⁴ and antitumor reagents (Scheme 1).⁵ As a result, many methodologies, including nucleophilic, electrophilic and radical trifluoromethylations, have been developed in the past decades.^{5c,6}

Among CF_3 -containing building blocks, α -trifluoromethyl benzyl halides or pseudo halides⁷ are readily available and have been widely used for the synthesis of molecules bearing CF_3 for medicinal chemistry and advanced functional materials.⁸ For examples, arylation of α -trifluoromethyl benzyl alcohol and arylation of α -trifluoromethyl benzyl tosylate have been achieved *via* Friedel–Crafts type reaction (Scheme 2a)⁹ and Suzuki-type coupling^{8g,h,10} respectively (Scheme 2b). However, Friedel–Crafts alkylation usually requires electron-rich arenes and may suffer from the formation of regioisomeric mixtures. Similarly, alkenylation of α -trifluoromethyl benzyl halides has been achieved *via* transition metal-catalyzed Heck reaction (Scheme 2c).¹¹ Besides, In catalyzed allylation of ketones containing α - CF_3

allyltrifluoroborates also offers the corresponding products.¹² But various limitations exist for transition metal-catalyzed cross-coupling reactions. Limitations include side reactions such as β -hydride elimination,¹³ requiring special catalysts or ligands, a lack of general and mild conditions, as well as high loading of catalysts (>5%).

Inspired by the pioneering works on transition metal-free Suzuki-type couplings by the groups of Tang, Wang, Ryu and Huang,^{7a–d,14} as well as our recent work,¹⁵ we are glad to report a general and efficient transition metal-free cross-coupling reaction between fluorinated benzyl electrophiles and alkenylboronic acids in the presence of the equivalent amount of alkali metal salts (Scheme 2d).

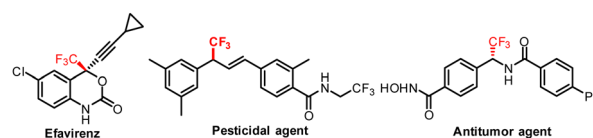
Initially, we started the transition metal-free cross-coupling reaction by using α -trifluoromethyl benzyl halides or pseudo halides **1** as electrophiles with alkenylboronic acid **2a** (Table 1). First, we investigated the reactions of α - CF_3 benzyl electrophiles containing various leaving groups (Table 1, entries 1–4) with boronic acid **2a** in the presence of alkali metal salt K_3PO_4 . Both α -trifluoromethyl benzyl bromide and tosylate, as well as methanesulfonate did not give any coupling product (Table 1, entries 1–3). To our delight, the desired product **3a** was obtained in 60% yield when α -trifluoromethyl benzyl triflate was used (Table 1, entry 4). On the other hand, no reaction occurred when less reactive styrylboronic ester **2b** was used, and potassium styryltrifluoroborate **2c** gave a low yield (Table 1, entries 5 and 6). Screening of alkali metal salts of different types (Table 1, entries 7–11) revealed metal phosphate is better than stronger bases (NaOt-Bu, NaOMe, NaOH) or weaker bases (K_2CO_3 and KF). Moreover, solvents screening (Table 1, entries

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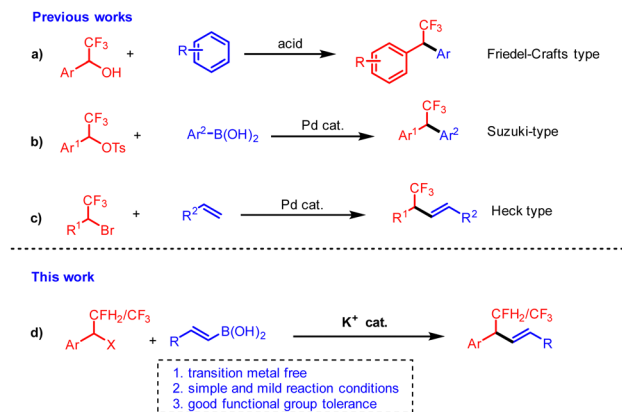
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Scheme 1 CF_3 -containing pharmaceutically active molecules.



Scheme 2 Literature background.

Table 1 Optimization of reaction conditions^a

Entry	X	2	Alkali metal	Solvent	Yield ^b (%)
1	Br	2a	K ₃ PO ₄	Tol	0
2	OTs	2a	K ₃ PO ₄	Tol	0
3	OMs	2a	K ₃ PO ₄	Tol	0
4	OTf	2a	K ₃ PO ₄	Tol	60
5	OTf	2b	K ₃ PO ₄	Tol	0
6	OTf	2c	K ₃ PO ₄	Tol	33
7	OTf	2a	K ₂ CO ₃	Tol	53
8	OTf	2a	KF	Tol	40
9	OTf	2a	NaOH	Tol	28
10	OTf	2a	NaOMe	Tol	7
11	OTf	2a	NaOtBu	Tol	8
12	OTf	2a	K ₃ PO ₄	PhCF ₃	56
13	OTf	2a	K ₃ PO ₄	DCE	70
14	OTf	2a	K ₃ PO ₄	THF	19
15	OTf	2a	K ₃ PO ₄	DMF	0
16 ^c	OTf	2a	K ₃ PO ₄	DCE	90
17 ^d	OTf	2a	K ₃ PO ₄	DCE	91
18 ^e	OTf	2a	K ₃ PO ₄	DCE	87
19	OTf	2a	—	DCE	0
20 ^f	OTf	2a	K ₃ PO ₄	DCE	88

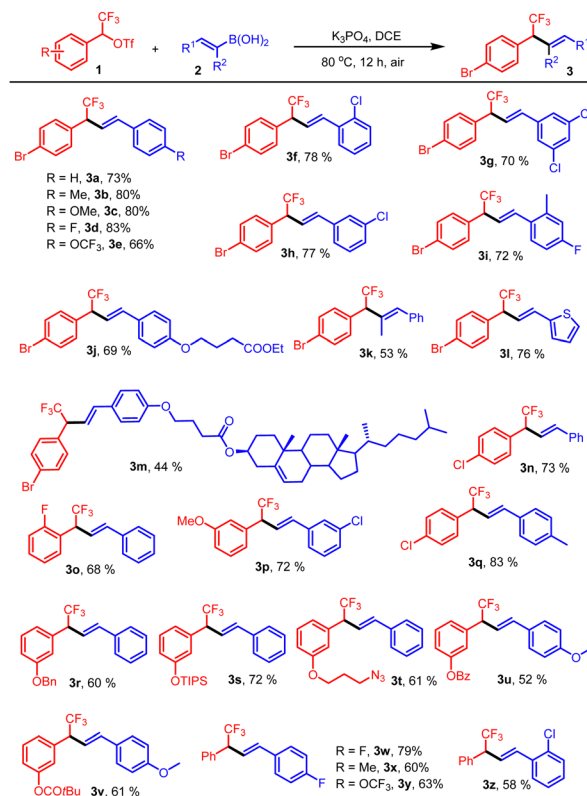
^a Conditions: **1** (0.1 mmol), **2** (0.15 mmol), alkali metal salt (0.2 mmol) in solvent (1 mL), 60 °C, 12 h. ^b All yields are determined by GC-MS. ^c The reaction was conducted at 80 °C. ^d The reaction was conducted at 100 °C. ^e The reaction was conducted at 80 °C under argon. ^f K₃PO₄ (0.1 mmol).

12–15) showed that DCE was the optimal solvent. And it should be noted that changing the solvent from low polarity solvents to more polar solvents such as DMF and THF resulted in significant decrease of the chemical yields (Table 1, entries 12–15). Additionally, the yield could be further improved when the reaction temperature was raised from 60 °C to 80 °C (Table 1, entry 16). However, further raising temperature to 100 °C or conducting the reaction under an argon atmosphere did not improve the reaction (Table 1, entries 17 and 18). Moreover, the coupling reaction can't proceed in the absence of alkali metal

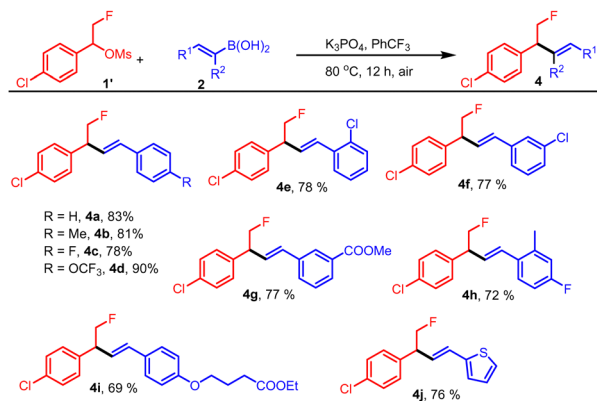
salts (Table 1, entry 19). Furthermore, the transformation was not hindered when decreasing the loading of K₃PO₄ from two equivalents to one equivalent (Table 1, entry 20).

With the optimized reaction conditions in hand, we examined the substrate scope and limitations of this transition metal-free protocol. First, we investigated the scope of alkenylboronic acids **2** by reacting with α -trifluoromethyl benzyl triflate **1a**. As showed in Table 2, diverse alkenylboronic acids **2** worked very well. For **2** with substituents at the *para* position of the phenyl ring, like methyl (Table 2, **3b**), fluorine (Table 2, **3d**), methoxy (Table 2, **3c**), trifluoromethoxy (Table 2, **3e**), ether (Table 2, **3j**), good yields were obtained regardless. For **2** with substituents at the *ortho* and *meta* position, the yields were slightly lower (Table 2, **3f–h**). Besides, di-substituted styrylboronic acids **2** were also suitable substrates (Table 2, **3g**, **3i**). Heterocycles such as thiophene substituted alkenyl boronic acids **2** (Table 2, **3l**) also worked very well. A slight decrease of chemical yield was observed for sterically hindered trisubstituted alkenyl boronic acids **2** (Table 2, **3k**). Furthermore, for substrates containing complex natural products like a steroid skeleton (Table 2, **3m**), this protocol worked very well, possibly due to mild reaction conditions.

Next, we investigated the substrate scope of α -trifluoromethyl benzyl triflates **1**. For **1** with substituents at *ortho*, *meta* and *para* positions of the phenyl ring (Table 3, **3n–3q**), moderate

Table 2 Coupling reaction between α -trifluoromethyl benzyl triflates and alkenylboronic acids

Conditions: **1** (0.2 mmol), **2** (0.3 mmol), K₃PO₄ (0.2 mmol) in DCE (1.5 mL), 80 °C, 12 h, air. All yields are isolated yields.

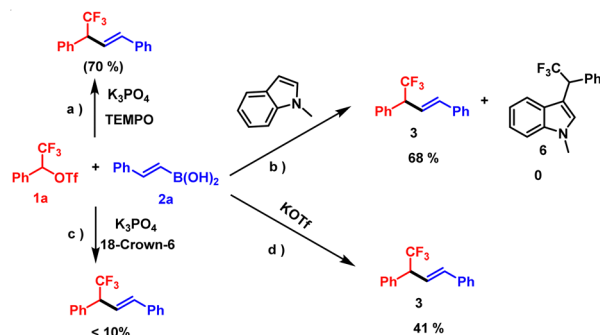
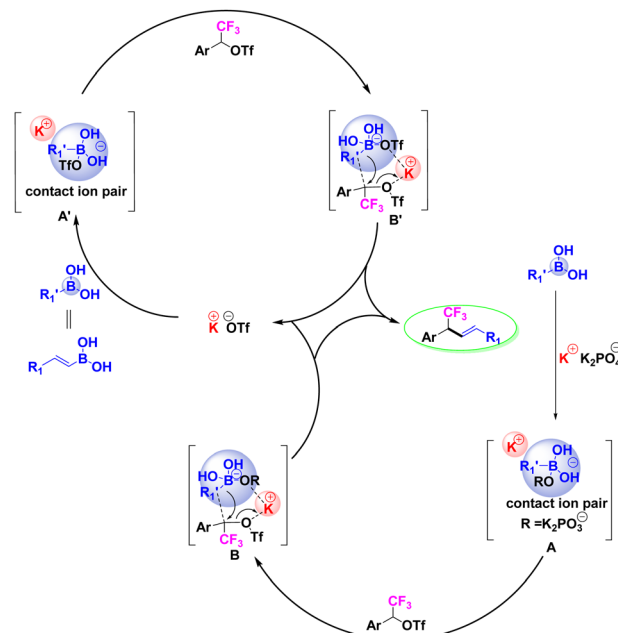
Table 3 Coupling reaction between α -monofluoromethyl benzyl methanesulfonates and alkenylboronic acids

Conditions: **1** (0.2 mmol), **2** (0.3 mmol), K_3PO_4 (0.2 mmol) in $PhCF_3$ (1.5 mL), $80^\circ C$, 12 h, air. All yields are isolated yields.

yields were obtained. Besides, the reaction system tolerated a variety of valuable functional groups including benzyl (Table 2, **3r**), azide (Table 2, **3t**), benzoyl (Table 2, **3u**), ester (Table 2, **3v**) and silyl groups (Table 2, **3s**). Then, we turned our attention to monofluoromethane substrates. After more optimization, α -monofluoromethyl benzyl methanesulfonates reacted smoothly with alkenylboronic acids to give the coupling products **4** in moderate to good yields (Table 3).

To better understand reaction pathways, we then moved our focus to the investigation of possible reaction pathways (Scheme 3). The reaction was not affected by both TEMPO (a radical quencher) and *N*-methylindole (an electron-rich aromatic compound)^{7a-c} (Scheme 3a and b). These results indicated that both radical intermediate or cationic intermediate were not likely and the reaction may not go through a radical mechanism or a S_N1 like mechanism. Furthermore, only trace product was detected when using K^+ chelator (18-crown-6) (Scheme 3c), which indicated that K^+ played an extremely important role, even participating in this transformation. In addition, the desired product **3** was obtained (Scheme 3d) when using KOTf instead of K_3PO_4 , which indicated that KOTf formed acted as a promoter for the conversion.

Based on the above experimental results, a proposed mechanism was given in Scheme 4. Firstly, the base (K_3PO_4) attacked

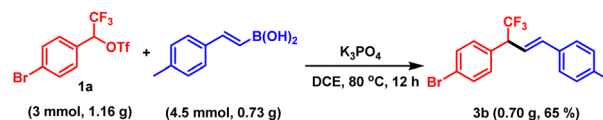
**Scheme 3** Investigation of reaction pathways.**Scheme 4** Proposed mechanism.

the alkenylboronic acid to form an ate type complex **A**, whose anionic nature led to enhanced nucleophilicity.¹⁶ When the reaction is conducted in non-polar solvents such as DCE, this complex is likely to exist as a contact ion pair.¹⁷ When complex **A** reacted with an sp^3 -carbon electrophile, a medium size cyclic intermediate **B** could form with the assistance of K^+ . Then, complex **B** underwent nucleophilic substitution, giving the cross-coupling product **3**. On the other hand, the formed KOTf functioned like the K_3PO_4 . Firstly, the KOTf attacked the alkenylboronic acid to form an ate type complex **A'**. Then, a medium size cyclic intermediate **B'** could form with the assistance of K^+ when the complex **A'** encountered an sp^3 -carbon electrophile. Lastly, complex **B'** underwent nucleophilic substitution, giving the cross-coupling product **3**.

Finally, to demonstrate the applicability of our strategy in synthesis, we conducted the transition metal-free cross coupling reaction using α -trifluoromethyl benzyl triflates **1a** as electrophiles in gram scale and comparable yields were obtained. (Scheme 5)

Conclusions

In conclusion, we have developed a general and efficient transition metal-free cross-coupling reaction between fluorinated benzyl electrophiles and alkenyl boronic acids with the assistance of alkali metal salts under simple and mild conditions. Other transition metal-free cross-coupling reactions are currently

**Scheme 5** Gram-scale synthesis.

being investigated in our laboratory and will be communicated in due course.

Author contributions

Wenna Xie: investigation, formal analysis, writing the original draft, resources. Shiwen Liu: data curation, methodology. Gerald B. Hammond: conceptualization, project funding. Bo Xu: validation, project funding.

Conflicts of interest

There are no conflicts to declare.

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